SPARTAN

SPondyloArthritis Research & Treatment Network

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SPARTAN NEWS

Greetings!

Greetings and best wishes as we enter a new year.

Importantly, the Governance Committee will be reviewing the SPARTAN membership list to determine those associate members requiring re-application of their membership. The review will determine if each associate member qualifies for full membership or whether they need to fulfill the requirements to continue to receive SPARTAN benefits, including reimbursement of annual meeting expenses. To see the requirements for full membership and associate membership, click HERE. It's a good time to consider engaging in some meaningful and exciting committee work to advance the spondyloarthritis agenda (and keep your SPARTAN membership active!) Trainees completing their fellowship should think about applying for associate membership--we'd love to have you!

Take note of the next SPARTAN annual meeting in Madison, WI, May 2 - 4 beginning with a Trainee Symposium and the general welcome reception and poster viewing. If you have fellows you would like to attend the meeting, now is the time to clear clinical schedules for those dates!

We just completed a provocative and efficient Board of Directors Strategic Planning session in Denver, have made substantial progress in laying the groundwork for the CLASSIC study to validate spondyloarthritis classification criteria, and are developing new funding announcements for trainees. This promises to be a very productive year for our organization!

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JOURNAL CLUB:
CRITICAL REVIEW OF THE LITERATURE

Riechers E, Baerlecken N, Baraliakos X, Achilles-Mehr Bakhsh K, Aries P, Bannert B, Becker K, Brandt-Jürgens J, Braun J, Ehrenstein B, Euler HH, Fleck M, Hein R, Karberg K, Köhler L, Matthias T, Max R, Melzer A, Meyer-Olson D, Rech J, Rockwitz K, Rudwaleit M, Schmidt RE, Schweikhard E, Sieper J, Stille C, von Hinüber U, Wagener P, Weidemann HF, Zinke S, Witte. T. Sensitivity and specifity of autoantibodies against CD74 in axial spondyloarthritis. Arthritis Rheumatol. 2018 Nov 12.

Anti-CD74 antibodies (Ab) were compared in patients with 1) early axial spondyloarthritis (axSpA) [n=100], 2) chronic back pain (CBP) <2 years duration [n=149], 3) ankylosing spondylitis for ≥10 years [n=50], and 4) serum donor with unknown back pain status [n=100]. For CD74 IgA Ab, the sensitivity for axSpA was 47%, the specificity was 95.3%, and the post-test probability was 33.3%. In comparison, HLA-B27 sensitivity, specificity, and post-test probability were 81%, 90%, and 28.2%. Both HLA-B27 and CD74 IgA Ab occurred in 35% of the axSpA group, and the post-test probability for the combination of IgA Ab and HLA-B27 was 80.2%. CD74 IgG Ab and IgA serum levels did not sufficiently differentiate between patients with and without axSpA. These data suggest that CD74 IgA Ab testing may be promising for diagnostic evaluations of axSpA, in combination with HLA-B27 testing. However, another study of CD74 Ab (de Winter et al. Arthritis Rheumatol 2018) reported much smaller differences with CD74 IgA Ab between early axSpA vs. CBP patients. The assays may have differed, since they were modified by investigators to address measurement limitations with soluble CD74 in newly collected vs. stored samples. Also, the axSpA population may not have been closely representative of the general axSpA population since participants were required to fulfill ASAS criteria and to have concordant interpretations of MRI sacroiliac joints between local and central readers.

Although this study was not designed to assess pathophysiology, there are several unanswered questions. Specifically, what is the potential mechanistic role in axSpA of CD74 Ab and the macrophage migration inhibitory factors (MIF) that bind to CD74 receptors? Does the IgA form of the antibody reveal its source (the gut mucosa)? When do CD74 Ab appear in the immune response? Are there relationships between CD74 Ab and axSpA duration, stage, or phenotype? Are there methodologic differences that influence results? Additional information addressing these questions will be useful in determining the clinical utility of CD74 Ab assessments in axSpA.

- Jessica Walsh, MD

Antoniou AN, Lenart I, Kriston-Vizi, J, Iwawaki T, Turmaine M, McHugh K, et al. Salmonella exploits HLA-B27 and host unfolded protein responses to promote intracellular replication. Ann Rheum Dis. 2019 Jan;78(1):74-82. doi: 10.1136/annrheumdis-2018-213532. Epub 2018 Oct 24.

HLA-B27 misfolding induces the unfolded protein response, which has been proposed to be an important aspect of the pathogenesis of axial spondyloarthritis. The unfolded protein response activates the x-box binding protein 1 (XBP-1). Accumulation of misfolded proteins in the endoplasmic reticulum also results in proteolytic cleavage of activating transcription factor 6 (ATF6), the cytosolic portion of which migrates to the nucleus where it acts a transcription factor. Further, it is known that having an HLA-B27 allele may increase an individual's susceptibility to develop reactive arthritis after Salmonella enterica infection or may increase the risk of Salmonella infection. In this study, Antoniou and colleagues evaluated the impact of HLA-B27 misfolding on endocellular growth and localization of S. enterica in infected epithelial cells.

The investigators generated epithelial cells that expressed physiological levels of HLA-B27 and controls that expressed HLA-B35. They demonstrated that, although both of these cell lines could present influenza nucleoprotein peptide 383-391 (NP383-391) to NP383-391-specific CD8+ cytotoxic T lymphocytes, the epithelial cells that expressed HLA-B27 were more susceptible to induction of the unfolded protein response than were those that expressed HLA-B35. Similarly, those epithelial cells expressing HLA-B27 were better able to support growth of S. enterica then were those expressing HLA-B35.

Activation of XBP-1 was necessary to support replication of S. enterica, since XBP-1-deficient murine embryonic fibroblasts contained significantly fewer bacteria during the replication stage than did wild type murine embryonic fibroblasts. Using thapsigargin (TPG) to reduce the unfolded protein response in HeLa cells prior to infection with S. enterica significantly increased the number of bacteria per cell but not the proportion of infected HeLa cells or induction of cell death during infection, compared to HeLa cells not pretreated with TPG. S. enterica had to be localized within a Salmonella-containing vacuole in order for the unfolded protein response-mediated effects on bacterial replication to occur. Using confocal microscopy, they observed S. enterica in Salmonella-containing vacuoles that were associated with the Golgi apparatus in HeLa cells expressing either HLA-B35 or a single chain trimer of HLA-B27 fused to beta-2 microglobulin and an HLA-B27-specific peptide derived from the influenza nucleoprotein. However, in HeLa cells expressing HLA-B27, which is more susceptible to induction of the unfolded protein response, they observed the bacteria to be located more peripherally within the cells.

The authors concluded that, by influencing the endoplasmic reticulum stress environment, HLA-B27 misfolding results in enhanced replication of S. enterica. During the early stages of infection, S. enterica is localized in Salmonella-containing vacuoles that are located adjacent to the nucleus and are associated with the Golgi apparatus. In the presence of misfolded HLA-B27, the bacteria may fail to form a Salmonella-containing vacuole or escape from the vacuole and redistribute throughout the cytoplasm. Thus, in the setting of misfolded HLA-B27, the Salmonella infection becomes more pronounced. However, this observation does not explain the mechanism by which Salmonella infection results in reactive arthritis. It will be important to assess the generalizability of this observation by studying it with other intracellular bacteria, such as Chlamydia, that are associated with reactive arthritis.

- Jonathan Kay, MD

ACR ABSTRACT REVIEW

Li Z, Guzman ED, Harris J, Akkoc N, Mahmoudi M, Breban M, Chou CT, Weisman M, Gensler LS, Ward M, Rahbar MH, Diekman LA, Kim TH, Leo P, Reveille JD, Wordsworth P, Brown M, Xu H. Genetic Risk Score Prediction in Ankylosing Spondylitis [abstract]. Arthritis Rheumatol. 2018; 70 (suppl 10). https://acrabstracts.org/abstract/genetic-risk-score-prediction-in-ankylosingspondylitis/.
Accessed December 30, 2018.

The premise for an interesting study by Matt Brown and colleagues involves the important concept that an early diagnosis of AS based on genetic risk might be more useful clinically than the usual operator-dependent data interpretation from clinical assessments or advanced imaging studies (MRI). Based on the theory that a polygenetic risk score, or GRS, that utilizes all of the known genome wide-significant associated SNP's to capture greater discriminatory capacity for

disease-risk prediction is better than simply using HLA-B27 status alone, Matt Brown and colleagues performed two large case-control series. One was based on AS of European descent (7,742 cases, 14,542 controls), the other based on East Asian-descent (6,001 AS, 4,943 controls); all subjects with AS had fulfilled Modified New York criteria (clear radiographic evidence of AS.) Results were displayed as ROC analyses with the area under the curve (AUC) indicating sensitivity and specificity. For the European GRS the AUC was 0.92, slightly better than using HLA-B27 status alone (0.87.) The AUC for the East Asian cohort was 0.95. Both models did reveal moderate discriminant capacity in other ethnic groups (Turkish, Iranian, and other European cohorts.) The investigators suggest that the performance of the GRS approaches, or even matches, the reference standard of an MRI which is estimated to perform with an AUC of 0.90 and is much more expensive to employ.

What are the take home messages here? Since all patients in these studies are radiographically confirmed cases, the majority of which are likely to have longstanding disease under management, can we really extrapolate these findings to the usual challenging diagnostic dilemma cases we see in the clinic today? Clearly it makes more sense that a 'yes/no' genetic score number will be easier to apply than a fuzzy interpretation of an MRI (are those margins really indistinct, who read these images?) from a conceptual point of view. However, using hard data from confirmed cases to interpret soft data from the clinic has bedeviled all of us since we initially learned almost a half-century ago in a small study from the Carl Pearson group at UCLA that of the multiple HLA antigens examined in 40 AS patients, 35 of the 40 patients were positive for W27, or 88%, compared to 8% W27 positivity in controls. What we need from Matt's group is an analysis of GRS performance in a cohort of suspicious very early AS cases where x-rays are not clear-cut, and MRI's are a matter of expert interpretation. Speaking to Matt about this issue, he states that an analysis of these patients would require an external gold standard for the diagnosis based on non-genetic and non-imaging means. Using only clinical criteria gives us a heterogeneous group without a good robust gold standard. Matt feels that his GRS are discriminatory for early axSpA that will eventually become radiographically confirmed AS; that is likely the take home message.

Etanercept and methotrexate as monotherapy or in combination to treat patients with psoriatic arthritis: primary results from a randomized, controlled, double-blind, phase 3 trial
Philip J. Mease,1 Dafna D. Gladman,2 David H. Collier,3 Christopher T. Ritchlin,4 Philip S. Helliwell,5 Lyrica Liu,3 Gregory Kricorian,3 James B. Chung3
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Given the plethora of new biologics for psoriatic arthritis (PsA), and the safety and efficacy of the initial biologics (remember, we are almost at 20 years' experience with them) the actual role of methotrexate (MTX) in the treatment of PsA needs to be re-examined. In truth, the efficacy of MTX in PsA is barely established from earlier small under-powered studies. Therefore, the impact of this well-designed study by Mease and colleagues, supported by Amgen, is especially welcome. There has never been a well-designed head to head study of methotrexate vs. a biologic up to this point, and a solid academic crew advising and carrying out this study with Amgen is to be commended. Active PsA patients never having received a biologic or methotrexate before were enrolled, thereby maximizing the potential benefit of the methotrexate arm, an important consideration. Three arms of the study were MTX, Etanercept (ETN), and the combination; the study was powered for all possible comparisons. The combo as well as ETN monotherapy alone showed greater efficacy than MTX alone, and MTX added to ETN did not improve efficacy of ETN. To support the benefit of ETN

monotherapy over MTX, less radiographic progression was seen in both ETN arms compared to MTX alone.

What is the take home message from this study? First, the authors should be congratulated for designing a study that did maximize the possibility to demonstrate the efficacy for the comparison arm (MTX alone) thereby addressing the usual criticism of drug-company sponsored studies. Most importantly, this study does place MTX in the role it likely deserves in PsA - to be used when biologics are either contra-indicated or not available, and the combination of MTX with a biologic in PsA is not supported in the literature. Although toxicities were no different among the arms of this particular study, long term use of MTX always poses a danger for the development of NASH or worse in psoriasis alone or in PsA.

- Michael H. Weisman, MD

LAURIE SAVAGE

With a heavy heart we are announcing to our membership the passing of Laurie Savage. SAA's in memorium pays an important tribute to the impact of Laurie on our world.

SPARTAN created the Laurie Savage Lifetime Achievement Award in 2017 in appreciation of Laurie's outstanding vision, exceptional dedication, and passionate commitment to the field of Spondyloarthris.

We will miss her in so many ways.

VISIT MADISON

On behalf of SPARTAN, we are very excited to bring the annual meeting to Madison May 2-4th, 2019. Here's my top five reasons to visit Madison!

1.There's much more to Madison than Wisconsin cheese (what's a cheese curd?) and beer, though there will be some of that too.
2. Madison often ranks at the top of "Best places to live" and "U.S. city for a perfect weekend getaway"
3. The city is situated on an isthmus between two beautiful, easily accessible lakes. It's a very green city, even in May.
4. Madison is an unlikely Foodie city. The freshness, variety and quality of food is astonishing for a city this size. The conference hotel is just off the main square, providing easy access to the Saturday farmer's market either before or after the morning session.
5. Finally, it's a University town. The Allen Centennial garden is a little gem on campus. The spirited students provide a boost of energy, as a walk along State Street will reveal.

We look forward to seeing everyone soon!

Judith Smith, MD, PhD

UPCOMING SPONDYLOARTHRITIS EVENTS

SAVE THE DATES!

ASAS Workshop
January 19-20, 2019
Amsterdam

SPARTAN Annual Education and Research Meeting
May 2-4, 2019
Madison
Registration

EULAR Annual European Congress of Rheumatology
June 12-15, 2019
Madrid

GRAPPA Annual Meeting and Trainee Symposium
July 11-13, 2019
Paris

ACR
November 8-13, 2019
Atlanta

SPARTAN Annual Education and Research Meeting
April 30 - May 2, 2020
Madison

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